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SEGMENTAL ANALYSIS OF RENAL GLUCOSE TRANSPORT IN YOUNG FEMALE RATS

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SUMMARY

1. Free-flow micropuncture studies were performed on twenty-seven young female Sprague–Dawley rats before and after 10% extracellular volume expansion to evaluate glucose reabsorption at the accessible sites of both surface and papillary nephrons.

2. In the distal nephron segments no significant glucose reabsorption was observed for the distal tubule and papillary collecting duct but significant difference in fractional glucose delivery was demonstrated between the bend of the Henle's loop and early distal tubule and between the late distal tubule and the base of the collecting duct.

3. Comparison of the fractional glucose delivery within the same nephron group for both superficial and juxtamedullary nephrons indicated that glucose reabsorption occurred at some sites beyond the bend of the Henle's loop.

4. Volume expansion inhibited glucose reabsorption in the proximal convoluted tubule, enhanced it in the segment between the late proximal and early distal tubules, but had no effect on glucose transport at further distal sites.

5. It is concluded that, in addition to the proximal tubule, the ascending loop of Henle or cortical collecting tubule may play a role in maintaining glucose-free urine under physiological conditions.

INTRODUCTION

It has been well documented that the major portion of filtered glucose is reabsorbed in the early proximal convoluted tubule (Rhode & Deetjen, 1968; Frohnert, Höhmann, Zweibel & Baumann, 1970) by a high-capacity and low-affinity glucose transport system (Tune & Burg, 1971; Von Baeyer, Von Conta, Haeberle & Deetjen, 1973; Barfuss & Schafer, 1981; Turner & Morgan, 1982). An additional mechanism to reabsorb glucose further is provided in the proximal straight tubule with low-capacity and high-affinity glucose transport (Tune & Burg, 1971; Von Baeyer, 1975; Barfuss & Schafer, 1981; Turner & Morgan, 1982) which may play a significant role in preventing overt glycosuria when early proximal reabsorption is inhibited (Wen, 1976; Wen, Boynar & Stoll, 1978; Wen & Stoll, 1979). As glucose reabsorption

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in the proximal segments alone is inadequate to account for virtually glucose-free urine (Rhode & Deetjen, 1968; Frohnert *et al.* 1970; Wen & Stoll, 1979; Bishop & Green, 1980, 1981), the loop of Henle (Wen *et al.* 1978) and collecting duct (Frohnert *et al.* 1970) have also been considered as the potential sites for glucose reabsorption. However, evaluation of glucose transport at these sites has been based on indirect information (Frohnert *et al.* 1970; Wen *et al.* 1978) and interpretation of such data has been hampered by the possible nephron heterogeneity in glucose transport. In an attempt to obtain further insight into the possible sites of glucose reabsorption in the distal nephron segments, we performed free-flow micropuncture studies at the accessible tubule sites of both superficial and deep nephrons to obtain a profile of glucose transport along the nephron. Our results indicate that glucose reabsorption does occur at some sites beyond the bend of Henle's loop for both nephron populations but not in the distal tubule or papillary collecting duct.

METHODS

Clearance and free-flow micropuncture studies were performed on twenty-seven young female Sprague–Dawley rats weighing 60–100 g. The animals had free access to food and water until the morning of the micropuncture study. These animals were prepared for micropuncture following anaesthesia with Inactin (5-ethyl-5-(1′-methyl-propyl)-2-thio-barbiturate; 100 mg/kg intraperitoneally). They were placed on a heated table to maintain body temperature at 37 °C using a rectal probe to monitor the temperature. A tracheal tube was inserted by tracheotomy to maintain an adequate airway. A carotid artery was cannulated for drawing of blood as well as for monitoring blood pressure and both jugular veins were cannulated for infusion of solutions and injection of 5% Lissamine Green dye for identification of the tubule sites. The bladder was exposed by a suprapubic incision and the right ureter was catheterized with PE-10 polyethylene tubing for collection of urine from the right kidney. The left kidney was exposed through a flank incision, dissected free of perirenal tissues and placed on a Lucite holder for immobilization. Micropuncture preparation of the renal papilla was made according to the method of Lacy & Jamison (1978). The renal papilla of the left kidney was exposed by lightly pulling the ureter to stretch the renal pelvis which was then severed at the level of the papillary tip. Retraction of the stretched renal pelvis automatically exposed the papilla and the residual pelvis was carefully trimmed. The exposed surfaces of the kidney and the renal papilla were covered with warm mineral oil to prevent evaporation. Surgical loss of fluid was replaced by I.V. infusion of pooled rat plasma in an amount equal to 1% of the body weight.

Clearance and micropuncture experiments were carried out in two phases: during the control phase and a second phase of extracellular volume expansion. In the control phase, following a priming I.V. injection of 0·5 ml 3% inulin in normal saline, the same solution was infused at 0·018 ml/min to sustain a constant plasma inulin concentration. Volume expansion in the second phase was carried out by I.V. infusion of normal saline at 0·42 ml/min until the expanded volume reached 10% of body weight. Thereafter, sustaining saline infusion was continued at an appropriate rate to replace the urine loss. About an hour was allowed for stabilization of the fluid balance before the second phase was resumed. Simultaneous clearance collection of urine was made at 30 min intervals for three or four periods in each phase with arterial blood samples drawn at the mid-point of each period.

The loops of Henle were identified by an I.V. injection of 0·05 ml 5% Lissamine Green which reached the loop approximately 30 s after the vascular blush. The loop segment was micropunctured near the bend using micropipettes with 6 μm o.d. tip, and a small droplet of coloured castor oil was injected into the loop to follow the course of tubule fluid flow. In the loop the oil droplet would either flow immediately toward the base or travel a short distance toward the tip and then turn back into the base of the papilla. Identification of the collecting duct was made easy by its rapid flow rate and by the immediate exit of the injected oil droplet to the tip of the papilla. The collecting duct was miropunctured at two sites using 12–14 μm o.d. micropipettes: a site as far up to the base

as could be reached and another site at the tip of the same tubule as determined by the exit of an oil droplet injected at the base.

Following completion of micropuncture of the papilla, the late proximal tubule and the early and late distal tubules of the superficial nephrons were also identified by I.V. injections of Lissamine Green dye and estimation of the transit time appropriate for the respective tubule sites. Lissamine Green injections were made only sparingly to minimize its effect on the tubule transport. Micropipettes with 12–15 μm o.d. were used for proximal micropuncture and those with 10–12 μm o.d. were used for the distal tubule. Tubule fluid collections were made after injection of an adequate amount of oil which was maintained distal to the puncture site to prevent retrograde collection of the tubule fluid. Tubule fluid collection was timed for calculation of the single nephron glomerular filtration rate (S.N.G.F.R.) using proximal tubule data for the superficial nephrons and those of the loops of Henle for the juxtamedullary nephrons.

The volume of tubule fluid samples was determined by measurement of the length of fluid column in a 1 μl constant-bore glass capillary using a Gaertner measuring microscope. Tubule fluid samples were analysed for inulin by the ultramicrofluorometric method of Vurek & Pegram (1966), and for glucose by a fluorometric hexokinase method (Stoll & Wen, 1978). Plasma and urine samples were analysed for inulin by an auto-analyser method (Steele, 1969), for glucose by a spectrophotometric hexokinase method (Peterson & Young, 1968), and for sodium and potassium by flame photometry.

All clearance and micropuncture data were analysed statistically using Student's t test for comparison of the mean data from each phase per experiment (Steel & Torrie, 1960).

RESULTS

Clearance data obtained from the contralateral kidney are summarized in Table 1. Mean glomerular filtration rate (G.F.R.) was 319 μl/min in the control phase and did not change significantly, at 347 μl/min after volume expansion. Urine flow increased markedly from 3·3 to 16·2 μl/min with volume expansion while plasma glucose concentration fell from 7·2 to 5·6 mmol/l due to haemodilution. Prominent natriuresis was also evident with the increase in absolute and fractional excretion of sodium from 0·6 to 3·2 μmol/min and from 1·1 to 6·7 %, respectively. Absolute glucose excretion was not affected by volume expansion at 9·6 and 10·9 nmol/min but fractional glucose excretion increased slightly from 0·4 to 0·6 %, reflecting the effect on plasma glucose concentration. Absolute and fractional excretion of potassium increased appropriately in response to volume expansion.

Micropuncture data at various nephron sites for both superficial and juxtamedullary nephrons are summarized in Table 2. Mean S.N.G.F.R. for the superficial nephrons was unchanged at 15·6 and 15·8 nl/min before and after volume expansion. Likewise, juxtamedullary S.N.G.F.R. remained unchanged at higher levels of 21·1 and 23·3 nl/min, respectively. Tubule fluid/plasma (TF/P) inulin ratios fell significantly after volume expansion at all tubule sites studied, indicating significant increases in fractional fluid delivery along the nephron. The TF/P glucose ratio was lowest in the late proximal tubule at 0·28 and highest at the bend of the Henle's loop at 0·80. Since the TF/P glucose ratio at the bend of the loop was higher than those at more distal nephron sites, and the corresponding TF/P inulin ratios at these distal sites were either unchanged or progressively increased, glucose must have been reabsorbed at some sites distal to the bend of the loop. Volume expansion raised TF/P glucose ratio in the late proximal tubule and reduced it at the bend of the loop and at the base and tip of the collecting duct. Fractional delivery of glucose increased significantly following volume expansion at the late proximal tubule and collecting duct. While

TABLE 1. Summary of clearance data before and after extracellular volume expansion

Exptl. phase	G.F.R. (μl/min)	V (μl/min)	P_G (mmol/l)	U/P_G	U_GV (nmol/min)	F.e.$_G$ (%)	P_{Na} (mmol/l)	$U_{Na}V$ (μmol/min)	F.e.$_{Na}$ (%)	P_K (mmol/l)	U_KV (μmol/min)	F.e.$_K$ (%)
Control	319	3·27	7·21	0·53	9·58	0·39	141	0·56	1·09	3·27	0·27	26·9
	±21	±0·49	±0·24	±0·06	±0·93	±0·02	±2	±0·12	±0·24	±0·13	±0·03	±3·8
Volume expansion	347	16·22**	5·60**	0·19**	10·88	0·60*	144	3·22**	6·65**	3·49	0·51**	47·1**
	±27	±2·00	±0·24	±0·03	±1·27	±0·07	±2	±0·47	±0·96	±0·15	±0·05	±4·1

Values are means±S.E. of means; clearance and urinary data are those of the contralateral kidney. G.F.R., glomerular filtration rate; V, urine flow; P, plasma; U, urine; F.e., fractional excretion; G, glucose; $*P < 0·05$; $**P < 0·01$.

TABLE 2. Summary of micropuncture data before and after extracellular volume expansion

Exptl. phase	S.N.G.F.R.$_{sf}$ (nl/min)	Late proximal tubule TF/P_{In}	Late proximal tubule TF/P_G	Late proximal tubule F.d.$_G$	Early distal tubule TF/P_{In}	Early distal tubule TF/P_G	Early distal tubule F.d.$_G$	Late distal tubule TF/P_{In}	Late distal tubule TF/P_G	Late distal tubule F.d.$_G$
Control	15·6	1·80	0·28	0·167	4·74	0·38	0·109	10·50	0·53	0·073
	±1·2	±0·11	±0·03	±0·016	±0·53	±0·05	±0·019	±1·91	±0·05	±0·010
Volume expansion	15·8	1·37*	0·41*	0·310*	2·31**	0·35	0·161	4·05**	0·42	0·108
	±2·0	±0·09	±0·05	±0·045	±0·19	±0·04	±0·022	±0·66	±0·09	±0·014
	S.N.G.F.R.$_{jm}$ (nl/min)	Loop of Henle TF/P_{In}	Loop of Henle TF/P_G	Loop of Henle F.d.$_G$	Base of collecting duct TF/P_{In}	Base of collecting duct TF/P_G	Base of collecting duct F.d.$_G$	Tip of collecting duct TF/P_{In}	Tip of collecting duct TF/P_G	Tip of collecting duct F.d.$_G$
Control	21·1	4·51	0·80	0·192	41·16	0·45	0·013	60·40	0·52	0·010
	±2·2	±0·56	±0·11	±0·022	±5·64	±0·06	±0·002	±5·90	±0·05	±0·001
Volume expansion	23·3	2·21**	0·50*	0·215	4·01**	0·25*	0·062*	6·52**	0·23**	0·043**
	±4·4	±0·27	±0·09	±0·051	±0·58	±0·07	±0·016	±0·94	±0·03	±0·006

Values are means±S.E. of means; S.N., single nephron; sf, superficial nephrons; jm, juxtamedullary nephrons; TF, tubule fluid; In, inulin; F.d., fractional delivery; others as in Table 1.

fractional glucose reabsorption in the proximal tubule was reduced from 83 to 69% by volume expansion, glucose reabsorption in the intermediate segment (between late proximal and early distal tubule) was enhanced from 5·8 to 14·9% of the filtered load.

Fig. 1 shows the changes in TF/P inulin and TF/P glucose ratios as well as those of fractional glucose delivery along the descending loop of Henle before and after volume expansion. In the control phase TF/P inulin and TF/P glucose ratios rose in proportion from the late proximal tubule to the bend of the loop (from 1·8 to 4·5 and from 0·28 to 0·80, respectively) indicating that water abstraction in the descending limb was primarily responsible for the rise in the TF/P glucose ratio. These changes were markedly blunted following volume expansion, suggesting a reduction

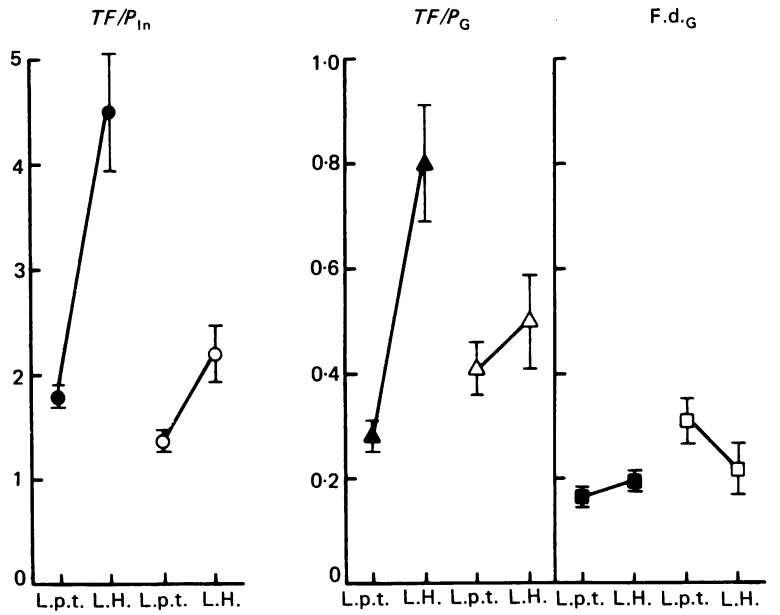

Fig. 1. Changes in tubule fluid/plasma (TF/P) inulin (In), TF/P glucose (G) ratios and fractional glucose delivery ($F.d._G$) in the descending loop of Henle, before and after volume expansion, assuming a relative nephron homogeneity. All points are means ± S.E. of means, with the filled symbols representing the control phase and the open symbols the volume expansion phase. L.p.t., late proximal tubule; L.H., loop of Henle.

in water abstraction. Absence of significant net glucose reabsorption in the descending limb before and after volume expansion was also indicated by the insignificant changes in fractional glucose delivery. However, these interpretations are subject to error if significant nephron heterogeneity of glucose transport exists between the superficial and juxtamedullary nephrons.

In order to circumvent the problem of nephron heterogeneity, fractional delivery of glucose was compared at the distal nephron sites for each nephron group (Fig. 2). Values for fractional delivery of glucose at the base of the collecting duct at 1·3 ± 0·2% (S.E. of mean) in the control phase and 6·2 ± 1·6% after volume expansion were significantly lower than the corresponding values of the late distal tubule for the superficial nephrons at 7·2 ± 1·0 and 10·8 ± 1·4%, respectively, as well as those at the

bend of the loop for the juxtamedullary nephrons at 19·2±2·2 and 21·5±5·1%, respectively. Thus, for both superficial and deep nephrons significant glucose reabsorption was demonstrated at a site prior to the base of the collecting duct and beyond the bend of the loop or the late distal tubule.

Fractional delivery and reabsorption of fluid and glucose in the superficial distal nephron segments are examined in Fig. 3. In the control phase significant fluid

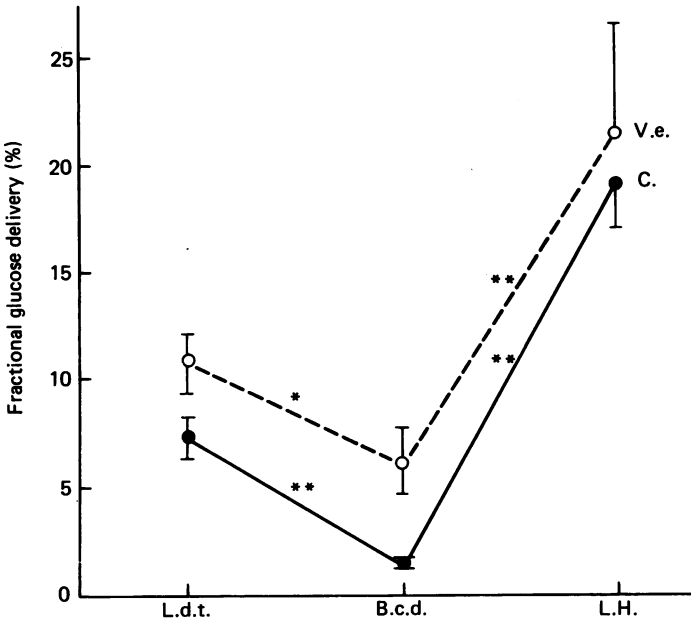

Fig. 2. Comparison of fractional glucose delivery in the distal nephron segments for the superficial (between late distal tubule (L.d.t.) and base of the collecting duct (B.c.d.)) and juxtamedullary nephrons (between loop of Henle (L.H.) and (B.c.d.)). Filled circles are mean values for the control phase (C.) and open circles are those of the volume expansion phase (V.e.). $*P < 0{\cdot}05$; $**P < 0{\cdot}01$; other abbreviations as in Fig. 1.

reabsorption was observed in all the distal nephron segments but fractional glucose delivery was significantly different only between the late distal tubule and the base of the collecting duct. No significant glucose reabsorption was observed in either the distal tubule or papillary collecting duct. Volume expansion markedly increased fractional fluid delivery at all distal nephron sites, and the difference in fractional fluid delivery between the late distal tubule and the base of the collecting duct was eliminated. This could be due to either a reduction of fluid reabsorption in the cortical collecting tubule or a disproportionally greater increase in fluid delivery from the juxtamedullary nephron to the base of the collecting duct. While fluid reabsorption in the distal tubule remained unchanged, that of the papillary collecting duct was greatly increased by volume expansion from 1·7 to 10·3% of the filtered load. In contrast, volume expansion had little effect on the pattern of fractional glucose delivery to the distal nephron sites except for the significant increases at the base and tip of the collecting duct. Again no significant glucose reabsorption could be demonstrated in the distal tubule or collecting duct. The differences in fractional

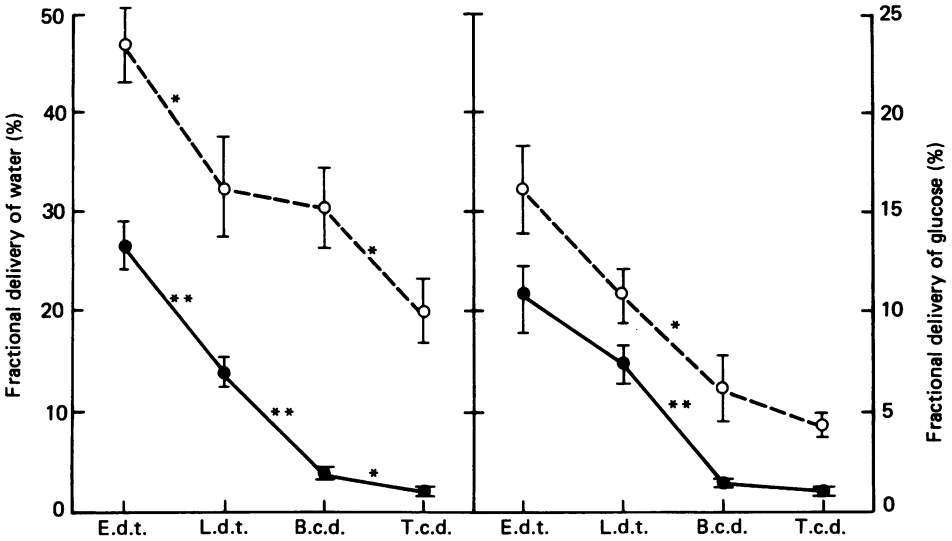

Fig. 3. Fractional delivery of water and glucose to the distal nephron segments before (filled circles) and after volume expansion (open circles). E.d.t., early distal tubule; T.c.d., tip of the collecting duct; other abbreviations as in Fig. 2.

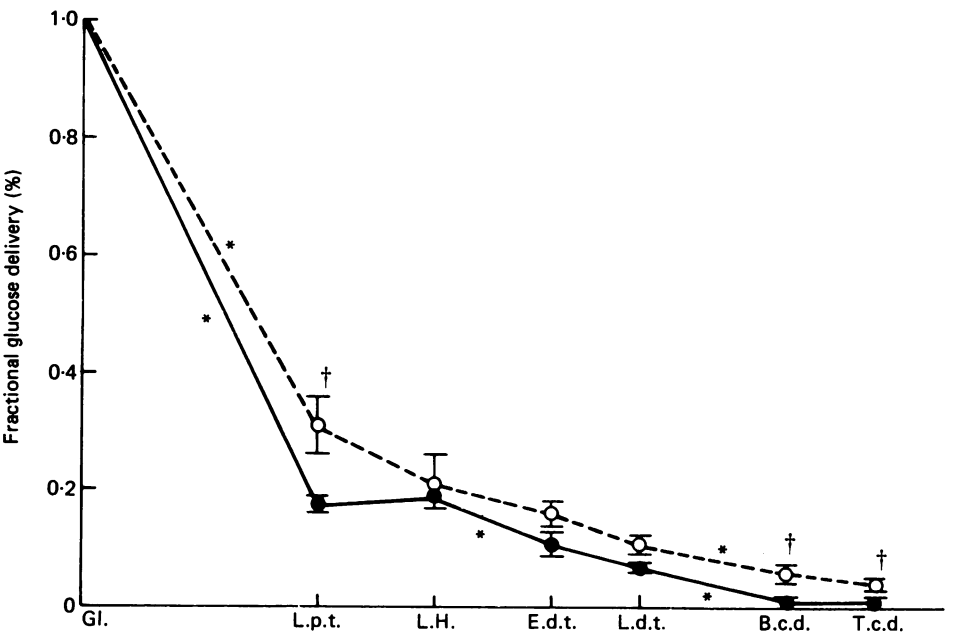

Fig. 4. Profile of fractional glucose delivery along the nephron sites before (filled circles) and after volume expansion (open circles). Gl., glomerulus; other abbreviations as in Figs. 1–3; $*P < 0{\cdot}05$ between the successive nephron sites; $\dagger P < 0{\cdot}05$ between the control and volume expansion phases.

glucose delivery between the late distal tubule and the base of the collecting duct before and after volume expansion were comparable at 6 and 5%, respectively.

Fig. 4 provides a profile of fractional delivery of glucose along the nephron sites before and after volume expansion. In both phases of the experiment, significant differences in fractional glucose delivery were observed between the glomerulus and late proximal tubule, between the late proximal and early distal tubule and between the late distal tubule and the base of the collecting duct. Volume expansion inhibited proximal reabsorption and it increased glucose reabsorption in the intermediate segment but no major changes in the pattern of fractional glucose delivery were observed in the distal nephron segments.

DISCUSSION

As fractional glucose excretion in the final urine is normally about 0·1–0·5% (Frohnert *et al.* 1970; Wen, 1976; Wen *et al.* 1978; Wen & Stoll, 1979; Bishop & Green, 1980) in the face of 90–98% fractional reabsorption in the proximal convoluted tubule (Frohnert *et al.* 1970; Wen, 1976; Wen *et al.* 1978; Wen & Stoll, 1979; Bishop & Green, 1981, 1983), glucose reabsorption at other sites must contribute significantly in order to maintain the urine essentially free of glucose (fractional glucose excretion less than 0·5%). Although glucose reabsorption in the 'intermediate segment' (between late proximal tubule and distal tubule) (Wen & Stoll, 1979; Wen, Boynar & Stoll, 1983) and 'short loops of Henle' (Von Baeyer, 1975; Bishop, Green & Thomas, 1981) has been shown previously, determination of the tubular location of glucose transport from micropuncture data is complicated by the possible nephron heterogeneity in glucose transport between the cortical and juxtamedullary nephrons.

Our micropuncture studies were carried out at most of the accessible nephron sites of both nephron populations to obtain a general profile of glucose transport along the nephron sites. Fractional glucose reabsorption at the late proximal tubule in our studies was 83·3 ± 8·5 (S.D.)% which is similar to our previous observations in the dog (Wen, 1976; Wen & Stoll, 1979) but considerably lower than the 94–98% reported by others in the rat (Frohnert *et al* 1970; Bishop & Green, 1981). There are multiple factors associated with our studies which could account for the lower value for fractional glucose reabsorption in the proximal tubule. First, young female rats were used in our studies while Frohnert *et al.* (1970) reported the data in older male rats. They observed that proximal glucose reabsorption in female rats was significantly lower than that in male rats. It is also possible that proximal glucose reabsorption is reduced in immature animals due to incomplete development of the tubule transport system since fractional proximal glucose reabsorption in the older female Sprague–Dawley rats weighing about 200 g was 90·4 ± 5·4 (S.D.)% (S.-F. Wen & N. R. McSherry, unpublished observation). Secondly, our rats had a relatively low mean proximal TF/P inulin of 1·8 and a high fractional sodium excretion of 1·1% in the control phase suggesting some degree of extracellular volume expansion which was induced during micropuncture preparation. We have previously shown that lower proximal sodium reabsorption is associated with lower proximal glucose reabsorption (Wen, 1976; Wen *et al.* 1978; Wen & Stoll, 1979).

Our studies showed that glucose reabsorption at tubule sites beyond the late

proximal convoluted tubule could occur in two segments as defined by free-flow micropuncture: (1) between the late proximal tubule and early distal tubule (intermediate segment) and (2) between the late distal tubule and the base of the collecting duct. The intermediate segment includes the proximal straight segment and the loop of Henle and it is generally thought that glucose transport in the intermediate segment represents exclusively that of the straight segment because it possesses the brush border and is known to have a limited capacity to reabsorb glucose (Tune & Burg, 1971; Barfuss & Schafer, 1981; Turner & Morgan, 1982). However, the possibility of glucose reabsorption in the ascending loop of Henle cannot be excluded. Our present micropuncture data at the bend of the loop showed that the mean value of 0·8 for the TF/P glucose ratio at this site was the highest among all the nephron sites examined in our studies. It was exceeded only by that of the initial proximal segment before substantial glucose reabsorption takes place. Such a pattern of TF/P glucose ratios in the distal nephron segments is in marked contrast to those of TF/P inulin which increased progressively toward the distal end of the nephron as fluid was reabsorbed. Thus, the high TF/P glucose ratio at the bend of the loop with its subsequent reduction in the more distal nephron segments, along with the unchanged or rising TF/P inulin ratio indicates that significant net glucose reabsorption must occur in the segments beyond the bend of the loop. In our studies we have circumvented the problem of nephron heterogeneity by comparing the fractional delivery of glucose between the late distal tubule and the base of the collecting duct for the superficial nephrons and between the bend of the loop and the base of the collecting duct for the juxtamedullary nephrons. In both of these nephron segments significant net glucose reabsorption was demonstrated, clearly indicating the existence of glucose transport in the distal nephron.

Certain nephron segments were excluded from the potential sites for glucose reabsorption in our studies. We showed that no significant net glucose reabsorption occurred in the distal convoluted tubule and papillary collecting duct even though significant fluid reabsorption was demonstrable in these segments. Thus, the ascending loop of Henle and the cortical collecting tubule appear to be potential sites for glucose transport. Indirect evidence supportive of loop glucose reabsorption has previously been obtained in the dog (Wen *et al.* 1978). Von Baeyer (1975) also reported glucose transport in the 'short loop of Henle' in the rat which was characterized by low capacity and high affinity and inhibitable by phlorhizin. In another rat microperfusion study, Bishop *et al.* (1981) also demonstrated that glucose transport in the 'short loops of Henle' was considerably different from that of the proximal convoluted tubule.

The evidence for glucose reabsorption in the cortical collecting tubule is also circumstantial. Bishop & Green (1983) showed that the recovery of radioactive glucose in urine following microinjection into the late distal tubule of virgin rats was incomplete, indicating absorption of about 10% of the injected glucose in one of the terminal segments of the nephron. On the other hand, similar microinjection studies in male rats reported by other authors showed no significant glucose absorption in the terminal nephron segments (Knight, Sansom & Weinman, 1977; Boonjarern, Mehta, Laski, Earnest & Kurtzman, 1977; Kramp & Lorentz, 1982). The discrepancy in these findings is difficult to explain but may be related to the difference in glucose transport between male and female rats.

As has been shown previously in the dog (Wen, 1976; Wen & Stoll, 1979), extracellular volume expansion significantly inhibited fluid and glucose reabsorption in the proximal convoluted tubule, indicating a close association between fluid and glucose transport in this segment. The resultant increase in glucose delivery out of the proximal convoluted tubule was nearly completely reabsorbed in the intermediate segment while fluid reabsorption in the latter segment remained unchanged. Von Baeyer (1975) also showed no relationship between glucose and fluid absorption in the short loop of Henle and glucose absorption could be increased without any change in volume absorption. In the segments beyond the bend of the loop, our studies showed that volume expansion had no significant effect on either the site or the magnitude of glucose reabsorption. This was in contrast to the marked increase in fluid delivery to and alterations in fluid reabsorption at these sites. Volume expansion greatly increased fluid delivery to the base of the collecting duct, resulting in the elimination of the difference in fluid delivery between the late distal tubule and the base of the collecting duct. It also increased fluid reabsorption in the papillary collecting duct. These effects of volume expansion on distal nephron segments have also been observed by Osgood, Reineck & Stein (1978). Thus, the effect of volume expansion on glucose transport in the distal nephron segments was clearly dissociated from that on fluid transport in our studies and suggests that nephron heterogeneity of volume expansion may not apply for glucose transport in this region.

In summary, our micropuncture studies on young female rats indicate that glucose reabsorption occurs not only in the proximal convoluted and straight segments but also at some sites beyond the bend of Henle's loop. In contrast to the proximal convoluted tubule, glucose reabsorption in the distal nephron segments is unaffected by extracellular volume expansion. The exact sites of glucose reabsorption in the distal nephron are unclear but could be either the ascending loop of Henle or the cortical collecting tubule. Although the magnitude of glucose reabsorption in these segments is small, it may also participate in the regulation of urinary glucose excretion to prevent overt glycosuria.

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